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Practical, efficient synthesis of *N*-mono-substituted *β*-amino tertiary thiols via reductive ring-opening of 3-thiazolines

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Abstract An efficient synthesis of *N*-mono-substituted *β*-amino tertiary thiols by reductive ring-opening of 3-thiazolines, obtained by use of the Asinger reaction, is described. This synthesis be regarded as a complementary approach for aminolytic ring-opening of thiiranes.

Keywords Asinger reaction · *β*-Amino tertiary thiols

A variety of methods are used to prepare *β*-amino ethanethiols. One of the most intriguing routes involves addition of amines to thiiranes in benzene (Scheme 1). The mechanism of the reaction involves SN_2-type nucleophilic attack of the amine on the thiirane. This reaction is usually suitable for addition of secondary amines to thiiranes, and *N*,*N*-bis-substituted *β*-amino tertiary thiols are obtained in good yield [1]. This procedure is not suitable for addition of primary amines to thiiranes to prepare the corresponding *N*-mono-substituted *β*-amino tertiary thiols, however, because of a competing reaction. Alternatives include addition of aromatic primary amines to thiiranes or activation by a thiophilic metal cation, for example silver nitrate [2].

We failed to obtain *N*-mono-substituted dimethylcysteamine by addition of primary amines to thiiranes. Unexpected compounds were obtained during our research on the Asinger reaction and further experiments proved the method enabled efficient synthesis of *N*-mono-substituted *β*-amino tertiary thiols.

The Asinger reaction is a simple but powerful multi-component reaction which has been used for synthesis of 3-thiazolines for more than three decades. A variety

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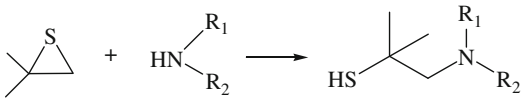
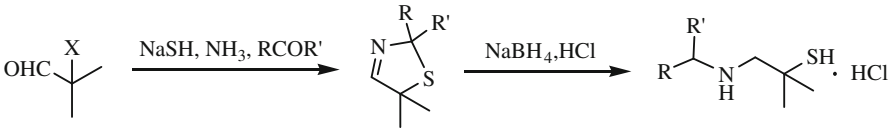
Scheme 1 Addition of amines to thiiranes





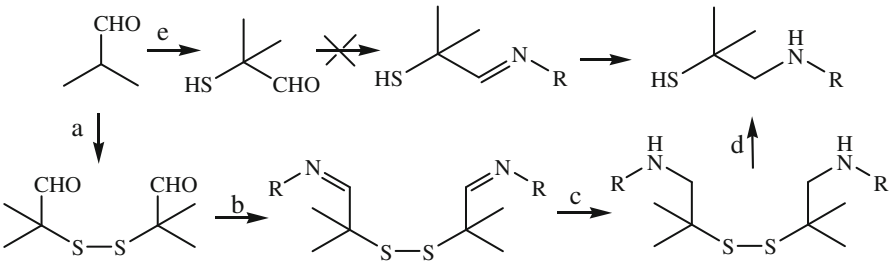
Scheme 2 Synthetic route

of sulfur-containing heterocyclic imines with different substituents have been synthesized by use of the modified Asinger reaction [3, 4]. More compounds have obtained by further treatment, for example addition, reduction, or ring-opening. For example, dimethylcysteamine hydrochloride has been obtained from 2-isopropyl-5,5-dimethylthiazolidine by use of $NaBH_4$ as reducing reagent and phenylhydrazine as carbonyl reagent [5, 6]. In our work we found that when the structure of the aldehyde or ketone was changed, a series of *N*-mono-substituted-2-amino-2,2-dimethylethanethiols were readily obtained. This result was not reported, and we found it could be used to obtain *N*-mono-substituted *β*-amino tertiary thiols.

The procedure is as follows. The 2-halo-2-methylpropanal, aqueous ammonia, sodium hydrogen sulfide, and aldehyde or ketone are reacted in a one-pot procedure. The 3-thiazolines were obtained as the main products in the reaction mixtures, in accordance with the Asinger reaction; the intermediate could also be separated and identified.[1] Without separation and further purification, the mixture was acidified to pH 2 with 2 M HCl, and $NaBH_4$ was added to the mixture. When the aqueous layer was concentrated the ring-opened product was formed (Scheme 2). Crystallization from a mixture of methanol and ether furnished the product, the *N*-substituted secondary amine 2,2-dimethylethanethiol hydrochloride salt. In a typical procedure, used to produce compound **3**, acetone was slowly added dropwise to a mixture of ammonia (25 %) and sodium hydrogen sulfide monohydrate with vigorous stirring at a temperature below 10 °C. A solution of 2-bromo-2-methylpropanal in dichloromethane was then added dropwise to the mixture over a period of 1.5 h. Evaporation of the organic solvents under reduced furnished the 3-thiazoline main product as a yellow oil. A suspension of the 3-thiazoline was reduced by $NaBH_4$ in acidic solution (pH 2), and the mixture was extracted twice with methyl tertiary butyl ether. The colorless aqueous solution was evaporated to dryness and the residue was recrystallized from a mixture of methanol and methyl tertiary butyl ether. The pure product was obtained as a white powder.

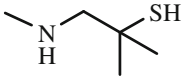
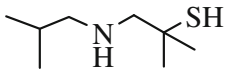
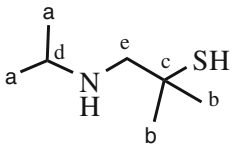
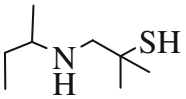
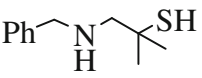
According to the mechanism of the Asinger reaction, 2-mercapto-2-methylpropanal was the intermediate; this was cyclized without separation and purification.

[1] Data for 3-thiazolines related to **3**: ^{1}H NMR ($CDCl_3$): 1.56 (s, 6H, C $(CH_3)_2$), 1.67 (s, 6H, $C(CH_3)_2$), 6.90 (s, H, =CH); related to **5**: ^{1}H NMR ($CDCl_3$): 1.57 (s, 6H, $C(CH_3)_2$), 5.50 (s, 1H, CH), 7.26 (s, 1H, =CH), 7.46–7.52 (m, 5H, Ph–H)



Scheme 3 Previous synthetic method: *a* S_2Cl_2 *b* NH_2R *c* $NaBH_4$ *d* $LiAlH_4$ *e* Br_2,NaSH

Table 1 The structures of the compounds[a]

Compound	Aldehyde (ketone)	Product	Yield (%)	Data
1	HCHO		62	^{1}H NMR (D_2O): 1.36 (s, 3H), 1.39 (s, 6H), 3.06 (s, 2H);^{13}C NMR (D_2O): 29.77, 40.84, 51.23, 68.82; MS: 120 ([M + H]); M.p: 158–160 °C
2	$(CH_3)CHCHO$		50	^{1}H NMR (D_2O): 0.92 (d, 6H), 0.97 (s, 6H), 1.96–1.98 (m, 1H), 2.83 (s, 2H), 2.94 (d, 2H), 3.15 (s, 2H);^{13}C NMR (D_2O): 19.18, 25.30, 29.15, 41.61, 55.45, 59.56; MS: 162 ([M + H]); M.p: 204–206 °C
3	CH_3COCH_3		42	^{1}H NMR (D_2O): 1.30 (s, 6H), 1.43 (s, 6H), 3.07 (s, 2H), 3.32–3.35 (m, 1H); ^{13}C NMR (D_2O): 17.95 (a), 29.18 (b), 41.66 (c), 52.01 (d), 56.64 (e); MS: 148 ([M + H]); M.p: 113–115 °C
4	$CH_3CH_2COCH_3$		42	^{1}H NMR (D_2O): 0.90 (t, 3H), 1.10 (d, 3H), 1.51 (s, 6H), 2.87–2.91 (m, 2H), 3.04 (s, 2H), 4.46–4.50 (m, 1H); ^{13}C NMR (D_2O): 9.24, 14.82, 25.02, 29.05, 41.62, 51.82, 57.12; MS: 162 ([M + H]); M.p: 223–225 °C
5	PhCHO		67	^{1}H NMR (D_2O): 1.31 (s, 6H), 3.03 (s, 2H), 4.19 (s, 2H), 7.40–7.43 (m, 5H). ^{13}C NMR (D_2O): 29.09, 41.32, 51.57, 58.57, 128.83, 129.32, 130.22, 132.59; MS: 196 ([M + H]); M.p: 166–168 °C

[a] ^{1}H NMR, ^{13}C NMR, MS, and M.p. data are listed. The atoms in compound **3** are labeled. Yields were calculated relative to 2-bromo-2-methylpropanal

In our work, 3-thiazolines were effective intermediates for mercapto group protection. The strongly acidic conditions also reduced polymerization during reduction and ring-opening. The mercapto group in the title compounds could be identified by use of an acidic solution of $NaNO_2$; a green color were observed. In a previous synthetic route starting from 2,2,5,5-tetramethyl-3,4-dithiahexane-1,6-dial a secondary amine was formed, with the disulfide bond being broken by use of a reducing agent, for example $LiAlH_4$ [7]. Compared with this method (Scheme 3), our method is much simpler.

In conclusion, there are several advantages to this procedure. First, the reaction can be performed cleanly, thus eliminating the hazards and odor associated with thiiranes. Second, the reaction can be regarded as a complementary approach for aminolytic ring-opening of thiiranes. Finally, the yield is moderate and the purity of the desired products is high, thus eliminating the need for chromatographic purification (Table 1).

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